

Are Corticosteroid Injections Associated with Secondary Adrenal Insufficiency in Adults With Musculoskeletal Pain? A Systematic Review and Meta-analysis of Prospective Studies

Running Title: Corticosteroid Injection and Secondary Adrenal Insufficiency

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Ethical approval was not sought for the present study. This systematic review was prospectively registered on PROSPERO (ID no: CRD42020193066) and reported according to the PRISMA statement.

This work was performed in York, Manchester, Keele, and Derby, UK.

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1 **Abstract**

2 *Background* There is concern about offering corticosteroid injections for musculoskeletal pain
3 because of the possibility of secondary adrenal insufficiency (SAI)

4 *Question/Purpose* In this systematic review and meta-analysis of prospective studies, we asked:
5 (1) Are corticosteroid injections associated with SAI as measured by 7-day morning serum
6 cortisol? (2) Does this association differ depending on whether the shot was administered in the
7 spine or the appendicular skeleton?

8 *Methods* We searched Allied and Complementary Medicine AMED, Embase, Emcare,
9 MEDLINE, CINAHL, and Web of Science from inception to 22nd January 2021. We retrieved
10 4303 unique records of which 17 were eventually included. Study appraisal was via the Downs
11 and Black tool, with an average quality rating of ‘fair’. A Grading of Recommendations,
12 Assessment, Development, and Evaluations assessment was conducted with the overall certainty
13 of evidence being low to moderate. Reflecting heterogeneity in the study estimates, a pooled
14 random-effects estimate of cortisol levels 7 days after corticosteroid injection was calculated.
15 Fifteen studies or subgroups (254 participants) provided appropriate estimates for statistical
16 pooling. 106 participants received an injection into their spine, and 148 participants received an
17 injection into the appendicular skeleton including the glenohumeral joint, subacromial bursa,
18 trochanteric bursa, and knee joint.

19 *Results* 7 days after corticosteroid injection the mean morning serum cortisol was 212 nmol/l
20 (95% CI, 133, 290), suggesting SAI was a possible outcome. There is a difference in risk of SAI
21 depending on whether the injection was in the spine or appendicular skeleton. For spinal

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22 injection the mean cortisol was 98 nmol/l (95% CI, 48, 149) suggesting SAI was likely. For
23 appendicular skeleton injection the mean cortisol was 311 nmol/l (95% CI, 213, 409) suggesting
24 HPA axis integrity was likely.

25 *Conclusion* Clinicians offering spinal injection should discuss the possibility of short-term SAI
26 with patients and decide together if the treatment remains appropriate and if mitigation strategies
27 are required. Clinicians offering appendicular skeleton injections should not limit care because of
28 concerns about SAI and clinical guidelines could be reviewed accordingly. Further research is
29 required to understand whether age and/or sex determine risk of SAI and what the clinical impact
30 of SAI is in patients undergoing spinal injection.

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31 Introduction

32 Musculoskeletal conditions, including osteoarthritis, tendon-related disorders, and low back pain,
33 are extremely common. In 2017 they were estimated to affect 18.8 million people across the
34 United Kingdom [58]. The World Health Organization estimates that approximately 1.71 billion
35 people worldwide have a musculoskeletal condition [63]. Corticosteroid injection is a very
36 common treatment for individuals experiencing musculoskeletal pain [3,14] and forms part of
37 the management of numerous conditions [2, 6, 10]. Synthetic corticosteroids mimic the action of
38 cortisol, an endogenous steroid hormone secreted by the adrenal gland, and influence
39 inflammatory pathways by binding to hormone receptor sites within cell nuclei to inhibit
40 inflammatory signalling and activating transcription of anti-inflammatory proteins [7]. Natural
41 levels of the hormone are controlled via a negative feedback loop by the hypothalamic-pituitary-
42 adrenal (HPA) axis [28] and one of the potential side effects of administering synthetic
43 glucocorticosteroid is suppression of this pathway, so called HPA axis suppression [41]. In its
44 most severe form, cortisol production can be completely suppressed, leading to secondary
45 adrenal insufficiency (SAI) [29]. There are numerous ways to diagnose SAI, including the long
46 and short ACTH stimulation tests, which directly assess the ability of the adrenal gland to secrete
47 cortisol in response to HPA axis stimulation; the long ACTH test exhibits a high likelihood ratio
48 for a positive test of 9.1 (44). Unfortunately, the use of these tests is sparse within the relevant
49 literature and many authors have instead focused on measuring morning serum cortisol via a
50 simple blood test [37], to assess peak level of circulating cortisol, from which to draw
51 conclusions about HPA axis function. While morning serum cortisol does not directly measure

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HPA axis function, several authors have established thresholds that have a high positive and negative predictive value for SAI [30,35,53].

SAI is associated with an increased frequency of infection compared to the general population, as well as an increased frequency of serious adverse events related to infection [47]. While SAI is a well-established risk associated with oral and inhaled corticosteroid use [38], whether or not the same risk exists with injected corticosteroids remains unclear. A previous study has identified a possible relationship between receiving a corticosteroid injection into a major joint and an increased susceptibility to influenza infection [55], a plausible mechanism for which would be SAI. However, the retrospective design of the study and the multiple possible confounders in play make the validity of the conclusions uncertain. The possibility that corticosteroid injections may cause SAI and increase susceptibility to infection has been a major preoccupation for clinicians and professional bodies throughout the COVID-19 pandemic and many clinical guidelines developed in response [4,5,34] have suggested limiting their use by, for example, reducing dosage, avoiding multi-site injections and providing alternative treatment. Given that reducing access to treatment is also likely to cause harm and that the World Health Organization believe COVID-19 will continue to be a challenge in the medium term [61], clarity regarding the issue of SAI after corticosteroid injection is urgently required. Current guidance has been based on expert opinion and engagement with a small number of primary studies. Therefore, a systematic review of the literature would seem appropriate to clarify the risk in relation to SAI. A key question around this issue is whether the risk of SAI differs depending upon whether the injection is delivered into the spine or the appendicular skeleton. Previous authors [15,36] have suggested that corticosteroid injection into the spine may be associated with more systemic

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uptake into the central nervous system via cerebrospinal fluid (CSF) because corticosteroids are thought to diffuse easily through the blood-CSF barrier [33]. We therefore considered that analyzing data by injection site was appropriate to detect if any such effect existed.

In this systematic review and meta-analysis of prospective studies, we therefore asked: (1) Are corticosteroid injections associated with SAI as indicated by 7-day morning serum cortisol? (2) Does this association differ depending on whether the shot was administered in the joints of the axial skeleton versus in the spine?

Materials and Methods

Search Strategy and Criteria

The following databases were searched from inception until 22nd January 2021 (Table 1): Allied and Complementary Medicine AMED (OVID), Embase (OVID), Emcare (OVID), MEDLINE (OVID), CINAHL, and Web of Science (Table 2). The search strategy was supplemented by manually searching the reference lists of included studies. Searches were not confined to English language sources and included conference proceedings; we did not search preprint servers (Supplemental Table 1; supplemental materials are available with the online version of *CORR*[®]).

All retrieved studies were imported into Mendeley and duplicates were removed electronically. Then, the studies were uploaded to Rayyan (rayyan.qcri.org) [43] to enable independent screening of the titles and abstracts by two reviewers (GW and BS). Studies were eligible for the review if they met our inclusion criteria as per our protocol (PROSPERO ID no: CRD42020193066). We included studies that evaluated morning serum cortisol in adults following corticosteroid injection for musculoskeletal pain, but excluded inflammatory joint pain

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(e.g. rheumatoid arthritis, axial spondyloarthropathies) because of the possible confounders at play in such populations. When duplicates were identified, these were marked as such during the review process. Subsequently, the full texts of potentially eligible studies were independently reviewed by two reviewers (GW and MM) to determine inclusion. Any disagreements were resolved through discussion (Fig. 1) [45]. Our search identified 5133 records for screening, reduced to 4303 once duplicate records were removed. Of these, 4231 were excluded during screening of the title and abstract. Full-text articles were obtained for the remaining 72 articles, and 52 of these were excluded. A further three studies were excluded because requests for additional data were not answered (Supplemental Table 2; supplemental materials are available with the online version of *CORR*[®]). The remaining 17 identified studies were eligible for inclusion in our review.

Data Collection Process

Data were extracted by the first author (GW) and entered into a bespoke form (not publicly available) in Microsoft Excel, agreed by the review team. This process was then verified by a second author (MM). If the data provided in the published articles were deemed insufficient to facilitate statistical analysis, the articles' corresponding authors were contacted via email to request additional information. If no response was received after 2 weeks, a reminder email was sent. If no response was received after 3 weeks, no further attempt was made to contact the authors.

Data Items

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Data extracted included study type, characteristics of participants, sample size, corticosteroid preparation, site of corticosteroid injection, corticosteroid dosage, and morning serum cortisol outcomes before and after corticosteroid injection.

Morning serum cortisol levels are obtained by a blood test. The measure may be obtained by any of the following recognized methods: Porter-Silber chromogens [46], competitive protein binding assay, fluorometric assay, radioreceptor assay, radioimmunoassay, or structurally based assays [37]. In the included studies, results were expressed in mcg/dl or nmol/l, depending on the method used. For this review, results were standardized to nmol/l using an online calculator (www.unitslab.com/node/110). The normal range is 275 nmol/l to 555 nmol/l [42]. For this review, a morning serum cortisol of less than 100nmol/l was considered highly predictive of SAI, previous authors having identified a positive predictive value of 93.2% for values below this cut off [53]. Additionally, a morning serum cortisol greater than 234.2 was considered highly predictive of HPA axis integrity, with previous authors having identified a negative predictive value of 95.8% for adrenal insufficiency for values above this cut off [30,35]. Because timepoints for morning serum cortisol blood draws were not uniform across studies, we clustered our reporting around the most consistently reported timepoint. For example, we reported cortisol levels for Day 6 or Day 8 in the absence of a value for Day 7.

Previous authors have described the absorption profile of different injected corticosteroids [8]; at 7 days post-injection, between 60% and 90% of the corticosteroid has been absorbed, depending on the type of corticosteroid and dosage. We therefore focused the presentation of our results at this critical timepoint, when substantial absorption of the corticosteroid would have occurred. To enable a comparison, we converted the corticosteroid preparation and dosage to an equivalent

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dosage of depomedrone using validated conversion tables [31]. Our review identified 17 prospective studies that measured morning serum cortisol levels after a corticosteroid injection for musculoskeletal pain (Table 3). Dosages of corticosteroid used ranged from the equivalent of 40 mg to 160 mg of depomedrone.

Quality Appraisal of Individual Studies

The Downs and Black quality appraisal checklist was used [12]. This checklist consists of 27 items and is valid and reliable for assessing the quality of randomized and non-randomized studies [12]. The quality appraisal was undertaken by one author (GW) and verified by another (MM). In this review, we used a modification commonly adopted by other authors [24, 39, 49] to determine the score assigned to the 27 items. A single point was awarded for studies that had sufficient power to detect a clinically important effect. A total score of 28 was obtained for each study, and the following grading system was used, as originally suggested by Hooper et al. [24]: excellent (24–28 points), good (19–23 points), fair (14–18 points), or poor (< 14 points).

Of the seventeen identified studies, one was rated as excellent, one as good, ten as fair, and five as poor (Table 4). The overall quality of evidence was therefore considered fair.

Synthesis of Results

Owing to the absence of the necessary data in a large number of studies, we could not calculate a pooled estimate of the mean change in cortisol from baseline to 7 days, which had been specified in our study's original protocol. We therefore used a random-effects model [54] to provide a pooled estimate of mean 7-day cortisol levels for studies that provided the required data, using a

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DerSimonian-Laird estimator [9] in the Meta-Essentials program [54]. A random-effects model was chosen in view of the level of heterogeneity of the study estimates; this allows the pooled estimate to better reflect the underlying variation in study contexts than a fixed-effect model and provides more conservative standard errors for the calculation of confidence intervals (CIs) [48]. Where there were distinct subgroups of participants in a study, we included separate estimates for these subgroups, rather than a single estimate for the study concerned, in the calculation of the pooled estimate. As well as calculating this estimate for all of the included studies, we derived separate estimates for spinal and peripheral injections. The associated 95% CI for the pooled estimates was calculated, as well as the 95% prediction interval. The prediction interval is the boundary within which 95% of the estimates of other similar studies would be expected to lie, and when there is any heterogeneity in study estimates, this interval will be wider than the corresponding 95% CI [25]. These interval estimates assume that point estimates from individual studies have an approximately normal distribution.

Heterogeneity or inconsistency of the study estimates was quantified by the I^2 statistic, which estimates the percentage of variability in individual study estimates attributable to heterogeneity rather than to random sampling error. Higgins et al. [23] suggested that values of I^2 up to 25% are low, those from 26% to 74% are moderate, and those above 75% are high. We also calculated the SD of study effects, represented by the T statistic. Heterogeneity of the pooled baseline and 7-day estimates was high: the I^2 statistic was 96.83% and 99.59% for baseline and 7 days, respectively. The T statistic was 51.80 and 91.88, respectively.

Additionally, in individual studies, we determined whether the estimates of morning cortisol levels lay within the normal range or in the ranges that suggest either possible or definite SAI.

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We were unable to provide an assessment of the role of age and sex of participants in the risk of SAI following corticosteroid injection because we did not have access to individual participant data from our included primary studies.

Certainty of Evidence

A Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) [17] assessment was undertaken to evaluate certainty in the available evidence. There was evidence of low certainty that corticosteroid injections for musculoskeletal pain were associated with possible SAI across all sites at 7 days. There was evidence of low-to-moderate certainty that corticosteroid injection into the spine was associated with SAI at 7 days. There was evidence of low-to-moderate certainty that corticosteroid injection into the appendicular skeleton was not associated with SAI at 7 days.

Ethical Approval

Because this is secondary research using publicly available data, ethical review was not required.

Primary and Secondary Study Outcomes

Our primary outcome was to establish if corticosteroid injection was associated with a reduction in morning serum cortisol at 7 days and if this was indicative of SAI. We derived a pooled estimate of morning serum cortisol at 7 days and associated 95% CI.

Our secondary outcome was to establish if there was a difference in the reduction in morning serum cortisol at 7 days when injecting the spine compared to the appendicular skeleton, and whether SAI was associated with either site of injection. We derived a pooled estimate of morning serum cortisol for both subgroups of patients and associated 95% CIs.

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Results

Secondary Adrenal Cortical Insufficiency 7 Days After Injection

The pooled estimate of the mean 7-day morning serum cortisol was calculated as 212 nmol/l (95% CI, 133, 290), suggesting possible SAI (Fig. 2). The associated 95% prediction interval was 0 to 424. The corresponding baseline estimate was calculated as 379 nmol/l (95% CI, 336, 422, with a 95% prediction interval of 260, 498). These calculations represented 254 participants in 15 studies, or subgroups within studies, and exclude the studies by Dickson et al. [11], Friedly et al. [15], Jacobs et al. [27], and Weyland et al. [60], for which 7-day morning serum cortisol levels and/or the associated SDs were missing.

We conducted a sensitivity analysis for outlier effects. This comprised recalculating the pooled mean estimates after excluding studies or subgroups whose 95% CI lay wholly outside the 95% CI for the pooled estimate. For 7-day morning cortisol levels the resulting estimate was very similar, at 215 nmol/l (95% CI, 142, 289); the corresponding baseline estimate was also similar, at 346 nmol/l (95% CI, 324, 368). Three studies included in the pooled analysis were rated as being of poor quality [13,18,32]. When these were excluded, the estimate of mean 7-day cortisol rose slightly to 229 nmol/l (95% CI, 137, 322). Similarly, when we excluded the two studies [13,22] in which the highest dosage of steroid (equivalent to 160mg dexamethasone) had been used, the estimated mean 7-day cortisol rose very slightly to 217 nmol/l (95% CI, 127, 307). We also ran a sensitivity analysis in which we omitted the very small study (n = 2) by Dubois et al. [13]; this had a negligible effect on the pooled estimates.

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222 *Comparing Injections in the Spinal versus the Appendicular Skeleton*

223 The pooled mean estimate for the eight studies or subgroups involving peripheral corticosteroid
 224 injections (148 participants) was 311 nmol/l (95% CI, 213, 409) and for the seven studies or
 225 subgroups involving spinal injection (106 participants) was 98 nmol/l (95% CI, 48, 149). The
 226 corresponding mean baseline estimates were 400 nmol/l (95% CI, 320, 480) and 345 nmol/l
 227 (95% CI, 312, 377). The decrease in cortisol levels was markedly greater for spinal injections
 228 than for peripheral injections and was highly suggestive of SAI for the spinal injection group,
 229 and conversely was highly suggestive of HPA axis integrity in the peripheral injection group.

230

231 **Discussion**

232 Corticosteroid injection is a widely used treatment for musculoskeletal pain, but the risk of SAI
 233 from this treatment has hitherto been unclear. Quantifying the risk of SAI is important because
 234 those experiencing it may have an increased susceptibility to infection and associated adverse
 235 outcomes [47]. Understanding whether a corticosteroid injection is likely to cause SAI will allow
 236 clinicians to engage in shared decision-making with patients about the potential risk and benefits
 237 of treatment. Given that several clinical bodies [4,5,34] have suggested limits to corticosteroid
 238 injection treatment during the COVID-19 pandemic based on limited evidence review, an urgent
 239 systematic appraisal of the evidence was needed to either validate or initiate review of these
 240 guidelines.

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241 *Limitations*

242 Our review was limited by a lack of between-group comparative studies available, meaning that
 243 we could not evaluate associated between-group effects. However, we were able to identify a
 244 large number of pre-test/post-test studies, and we were able to derive baseline and 7-day
 245 estimates. All studies demonstrated a reduction in morning serum cortisol at 7 days, indicating an
 246 association between lower morning serum cortisol level at 7 days and corticosteroid injection,
 247 albeit it with less certainty than if between-group comparisons against a control condition had
 248 been available.

249 A further limitation of the review was the reliance in many of the primary studies on morning
 250 serum cortisol as an outcome measure for HPA axis integrity. As we have discussed, morning
 251 serum cortisol is not a direct indicator of HPA axis integrity, but previous authors have identified
 252 cut-off values where morning serum cortisol has a high positive predictive value [53] and a high
 253 negative predictive value [30,35] for SAI. These values have been validated against ACTH
 254 stimulation testing, which itself has been shown to exhibit a good likelihood ratio for predicting
 255 SAI [44]. In this review we interpret our results using these previously validated thresholds for
 256 morning serum cortisol to decide if SAI is likely or unlikely, and although the presented morning
 257 serum cortisol figures do not themselves directly assess HPA axis integrity, we believe that our
 258 conclusions are robust.

259 Our review was also limited because of how the results of the primary studies were reported; we
 260 were unable to evaluate whether sex or age was a risk factor for SAI, as we did not have access
 261 to individual patient data. A previous study of 143 healthy adults [50] has demonstrated that both
 262 factors determine the secretory profile of cortisol for individuals. It may therefore be the case
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that risk of SAI after corticosteroid injection could increase depending on the age and sex of the patient. However, further empirical data are required to confirm this.

Although our findings do signal that SAI is likely at 7 days following spinal injection, it is unclear what the implications of this are clinically. It has been established that serum cortisol secretion is upregulated in response to viral infection, and that frequent modulation of this occurs over the course of infection, suggesting that cortisol is involved in tailoring the immune system response to the infection [41, 51]. A previous study has shown an increased risk of infection and associated adverse outcomes in those experiencing SAI [47]. However, it is not clear whether the transient SAI associated with spinal corticosteroid injection confers clinical risk and further empirical data are required to confirm this.

Secondary Adrenal Insufficiency 7 Days After Injection

Across all pooled studies we found that the point estimate of morning serum cortisol was in the range where SAI was possible but was above our defined threshold for likely SAI, and below our defined threshold for likely HPA axis integrity. However, our estimates for pooled spinal and appendicular skeleton injection lead to rather different conclusions regarding SAI at 7 days following treatment and are therefore more informative for clinical practice than the pooled estimate. Clinicians should therefore acknowledge that SAI is a possibility 7 days following corticosteroid injection but tailor their approach depending upon the site of injection as detailed below.

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282 *Comparing Injections in the Spinal versus the Appendicular Skeleton*

283 Our results suggest that spinal injection is likely to be associated with SAI seven days after
 284 administration. Clinicians should therefore use this information to consider whether such
 285 injection confers additional risk on their patient. For example, when considering the increased
 286 risk of infection associated with SAI clinicians may wish to account for various other factors
 287 before deciding with the patient how best to proceed. For COVID-19 this assessment may take
 288 account of the patient's age and comorbidities through the use of a risk stratification tool such as
 289 that developed by the British Medical Association [52], the patient's vaccination status, and
 290 whether there are any variants of concern currently in circulation. In the case of influenza both
 291 age and multimorbidity are predictors of mortality and morbidity [62]. If patients are considered
 292 to be at risk, shared decision making should take place to consider whether alternative treatment
 293 options are available, or whether the treatment could take place with appropriate risk mitigation
 294 strategies in place. Risk mitigation could take the form of those suggested in the National
 295 Institute for Clinical Excellence guidance on arranging planned care [40] and the use of personal
 296 risk mitigation strategies such as self-isolation after the procedure, mask wearing and/or social
 297 distancing.

298 Conversely, our data suggest that those undergoing injection in the appendicular skeleton are
 299 unlikely to experience SAI as a result of their treatment. Clinicians should therefore continue to
 300 offer corticosteroid injection into the appendicular skeleton and are unlikely to need to limit its
 301 use. The only exception to this might be if the patient is on concurrent steroid therapy by another
 302 route (for example inhaled steroids for asthma) as concurrent steroid therapies are likely to
 303 increase risk.

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304 *Conclusion*

305 Our review has found evidence of low to moderate certainty that spinal corticosteroid injections
306 are likely to be associated with SAI 7 days after administration, but that corticosteroid injections
307 of the appendicular skeleton are likely to be associated with HPA axis integrity 7 days after
308 administration. Our sensitivity analyses do not materially alter our conclusions. Clinicians should
309 use this information to inform shared decision making with patients considering corticosteroid
310 injection for musculoskeletal pain. Clinicians offering spinal injection should consider the risk of
311 SAI to an individual patient before providing treatment. Clinicians offering injection into the
312 appendicular skeleton should not limit care because of concerns about SAI. Current policy
313 guidance should be reviewed in light of these findings and reflect the different risk profiles of
314 spinal and appendicular skeleton injection for SAI.

315 While this review signals that SAI is likely 7 days after spinal injection, whether or how this
316 might manifest clinically is not understood. Further research is required to understand the
317 frequency and clinical course of SAI following corticosteroid injection of the spine. Further
318 research is also required to understand if age and/or sex are risk factors for developing SAI after
319 corticosteroid injection.

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References

1. Abdul AJ, Ghai B, Bansal D, Sachdeva N, Bhansali A, Dhatt SS. Hypothalamic pituitary adrenocortical axis suppression following a single epidural injection of methylprednisolone acetate. *Pain Physician*. 2017;20:E991–E1001.
2. Bateman M, McClymont S, Hinchliffe SR. The effectiveness and cost of corticosteroid injection and physiotherapy in the treatment of frozen shoulder – a single-centre service evaluation. *Clin Rheumatol*. 2014;33:1005–1008.
3. Bateman M, Titchener AG, Clark DI, Tambe AA. Management of tennis elbow: a survey of UK clinical practice. *Shoulder Elbow*. 2019;11:233–238.
4. British Orthopaedic Association. Management of patients with musculoskeletal and rheumatic conditions who: are on corticosteroids; require initiation of oral/IV corticosteroids; require a corticosteroid injection. Available at: <https://www.boa.ac.uk/uploads/assets/3767f092-abfb-40c8-bab2c711a81306d5/MSKcorticosteroidguidance.pdf>. Accessed 25th January 2021.
5. British Rheumatology Society. Clinical guide during the COVID-19 pandemic for the management of patients with musculoskeletal and rheumatic conditions. Available at: https://www.rheumatology.org.uk/Portals/0/Documents/COVID-19/MSK_rheumatology_corticosteroid_guidance.pdf. Accessed online 25th January 2021
6. Chesterton LS, Blagojevic-Bucknall M, Burton C, et al. The clinical and cost-effectiveness of corticosteroid injection versus night splints for carpal tunnel syndrome

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(INSTINCTS trial): an open-label, parallel group, randomised controlled trial.

Lancet.2018;392:1423–1433.

7. Coutinho AE, Chapman KE. The anti-inflammatory and immunosuppressive effects of glucocorticoids, recent developments and mechanistic insights. *Mol Cell Endocrinol*. 2011;335:2–13.
8. Derendorf H, Möllmann H, Grüner A, Haack D, Gyselby G. Pharmacokinetics and pharmacodynamics of glucocorticoid suspensions after intra-articular administration. *Clin Pharmacol Ther*. 1986;39:313–317.
9. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trial*. 1986;7(3):177–188.
10. Deyle GD, Allen CS, Allison SC, et al. Physical therapy versus glucocorticoid injection for osteoarthritis of the knee. *N Engl J Med*. 2020;382:1420–1429.
11. Dickson RR, Reid JM, Nicholson WT, Lamer TJ, Hooten WM. Corticosteroid and cortisol serum levels following intra-articular triamcinolone acetonide lumbar facet joint injections. *Pain Pract*. 2018;18:864–870.
12. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health*. 1998;52:377–384.
13. Dubois EF, Wagemans MF, Verdouw BC, et al. Lack of relationships between cumulative methylprednisolone dose and bone mineral density in healthy men and postmenopausal women with chronic low back pain. *Clin Rheumatol*. 2003;22:12–17.

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14. French HP, Woodley SJ, Fearon A, O'Conner L, Grimaldi A. Physiotherapy management of greater trochanteric pain syndrome (GTPS): an international survey of current physiotherapy practice. *Physiotherapy*. 2020;109:111–120.
15. Friedly JL, Comstock BA, Heagerty PJ, et al. Systemic effects of epidural steroid injections for spinal stenosis. *Pain*. 2018;159:876–883.
16. Guaraldi F, Gori P, Calderoni M, et al. Comparative assessment of hypothalamic-pituitary-adrenal axis suppression secondary to intrabursal injection of different glucocorticoids: a pilot study. *J Endocrinol Invest*. 2019;42:1117–1124.
17. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336:924–926.
18. Habib G, Artul S, Chernin M, Akim G. The effect of intra-articular injection of betamethasone acetate/betamethasone sodium phosphate at the knee joint on the hypothalamic-pituitary-adrenal axis: a case-controlled study. *J Investig Med*. 2013;61:1104–1107.
19. Habib G, Elias S, Abu-Elhaija M, et al. The effect of local injection of methylprednisolone acetate on the hypothalamic-pituitary-adrenal axis among patients with greater trochanteric pain syndrome. *Clin Rheumatol*. 2017;36:959–963.
20. Habib G, Jabbour A, Artul S, Hakim G. Intra-articular methylprednisolone acetate injection at the knee joint and the hypothalamic-pituitary-adrenal axis: a randomized controlled study. *Clin Rheumatol*. 2014;33:99–103.

AU: Please do not delete query boxes or remove line numbers; ensure you address each query in the query box. You may modify text within selected text or outside the selected text (as appropriate) without deleting the query.

21. Habib G, Khatib M, Sakas F, Artul S. Pre-injection of hyaluronic acid does not affect the systemic effects of intra-articular depot betamethasone injection at the knee joint. *Clin Rheumatol*. 2017;36:217–221.
22. Habib G, Khazin F, Jabbour A, Chernin, et al. Simultaneous bilateral knee injection of methylprednisolone acetate and the hypothalamic-pituitary adrenal axis: a single-blind case-control study. *J Investig Med*. 2014;62:621–626.
23. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analysis. *BMJ*. 2003;327:557–560.
24. Hooper P, Jutai JW, Strong G, Russell-Minda E. Age-related macular degeneration and low-vision rehabilitation: a systematic review. *Can J Ophthalmol*. 2008;43:180–187.
25. IntHout J, Ioannidis JPA, Rovers MM, Goeman JJ. Plea for routinely presenting prediction intervals in meta-analysis. *BMJ Open* 2016;6:e010247.
26. Iranmanesh A, Gullapalli D, Singh R, Veldhuis J. Hypothalamo-pituitary-adrenal axis after a single epidural triamcinolone injection. *Endocrine*. 2017;57:308–313
27. Jacobs S, Pullan PT, Potter JM, Shenfield G. Adrenal suppression following extradural steroids. *Anaesthesia* 1983;38:953–956.
28. Kadmiel M, Cidlowski JA. Glucocorticoid receptor signaling in health and disease. *Trends Pharmacol Sci*. 2013;34:518–530.
29. Laugesen K, Broersen LHA, Hansen SB, Dekkers OM, Sørensen HT, Jorgensen JOL. Management of endocrine disease: Glucocorticoid-induced adrenal insufficiency: replace while we wait for evidence? *Eur J Endocrinol*. 2021;184:R111–122.

AU: Please do not delete query boxes or remove line numbers; ensure you address each query in the query box. You may modify text within selected text or outside the selected text (as appropriate) without deleting the query.

30. Lee MT, Won JG, Lee TI, Yang HJ, Lin HD, Tang KT. The relationship between morning serum cortisol and the short ACTH test in the evaluation of adrenal insufficiency. *Zhonghua Yi Xue Za Zhi (Taipei)*. 2002;65:580–587.
31. Mager DE, Lin SX, Blum RA, Lates C, Jusco W. Dose equivalency evaluation of major corticosteroids: pharmacokinetics and cell trafficking and cortisol dynamics. *J Clin Pharmacol*. 2003;43:1216–1227.
32. Maillefert JF, Aho S, Huguenin M, et al. Systemic effects of epidural dexamethasone injections. *Rev Rhum Engl Ed*. 1995;62:429–432.
33. Mason BL, Pariante CM, Jamel S, Thomas SA. Central nervous system (CNS) delivery of glucocorticoids Is fine-tuned by saturable transporters at the blood-CNS barriers and nonbarrier regions. *Endocrinology*. 2010;151:5294–5305.
34. Miller DC, Patel J, Gill J, Mattie R, Saffarian M, Schneider BJ, Popescu A, Babaria V, McCormick ZL. Corticosteroid injections and COVID-19 infection risk. *Pain Med*. 2020;21:1703–1706.
35. Montes-Villarreal J, Perez-Arredondo LA, Rodriguez-Gutierrez R, et al. Serum morning cortisol as a screening test for adrenal insufficiency. *Endocr Pract*. 2020;26:30–35.
36. Moon HJ, Choi KH, Lee SI, Lee OJ, Shin JW, Kim TW. Changes in blood glucose and cortisol levels after epidural or shoulder intra-articular glucocorticoid injections in diabetic or nondiabetic patients. *Am J Phys Med Rehabil*. 2014;93:372–378.
37. Moore A, Aitken R, Burke C, et al. Cortisol assays: guidelines for the provision of a clinical biochemistry service. *Ann Clin Biochem*. 1985;22:435–445.

AU: Please do not delete query boxes or remove line numbers; ensure you address each query in the query box. You may modify text within selected text or outside the selected text (as appropriate) without deleting the query.

38. Mortimer KJ, Tata LJ, Smith CJ, et al. Oral and inhaled corticosteroids and adrenal insufficiency: a case-control study. *Thorax*. 2006;61:405–408.
 39. Morton S, Barton CJ, Rice S, Morrissey D. Risk factors and successful interventions for cricket-related low back pain: a systematic review. *Br J Sports Med*. 2014;48:685–691.
 40. National Institute for Health and Care Excellence. COVID-19 rapid guideline: arranging planned care in hospitals and diagnostic services (NG179). Available at: <https://www.nice.org.uk/guidance/NG179>. Accessed 26th January 2021.
 41. Nicolaides NC, Pavlaki AN, Maria Alexandra MA, Chrousos GP. Glucocorticoid therapy and adrenal suppression. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, et al., eds. *Endotext*. MDText.com, Inc.; 2000.
 42. Nieman L. Measurement of cortisol in serum and saliva. Available: www.uptodate.com. Accessed 20th September 2021.
 43. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan – a web and mobile app for systematic reviews. *Syst Rev*. 2016;5:210.
 44. Ospina NS, Nofal A, Bancos I, et al. ACTH stimulation tests for the diagnosis of adrenal insufficiency: systematic review and meta-analysis. *J Clin Endocrinol Metab*. 2016;101:427–34.
 45. Page M, Moher D, Bossuyt P, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ*. 2021;32:n160.
 46. Porter C, Silber R. A quantitative colour reaction for cortisone and related 17,21-dihydroxy-20-ketosteroids. *J Biol Chem*. 1950;185:201–207.
- AU: Please do not delete query boxes or remove line numbers; ensure you address each query in the query box. You may modify text within selected text or outside the selected text (as appropriate) without deleting the query.**

47. Quinkler M, Murray RD, Zhang P, et al. Characterization of patients with adrenal insufficiency and frequent adrenal crises. *Eur J Endocrinol*. 2021;184:761–771.
48. Raudenbusch SW. Analyzing effect sizes: random effects models. In: Cooper H, Hedges LV, Valentine JC (eds) *The Handbook of Research Synthesis and Meta-analysis*. New York: Russell Sage Foundation, 2009: 279–294.
49. Richmond SA, Fukuchi RK, Ezzat A, Schneider K, Schneider G, Emery C. Are joint injury, sport activity, physical activity, obesity, or occupational activities predictors for osteoarthritis? A systematic review. *J Orthop Sports Phys Ther*. 2013;43:515–524.
50. Roelfsema F, van Heemst D, Iranmanesh A, Takahashi P, Yang R, Veldhuis J. Impact of age, sex and body mass index on cortisol secretion in 143 healthy adults. *Endoc. Connect*. 2017;7:500–509.
51. Silverman M, Pearce B, Biron C, Miller A. Immune modulation of the hypothalamic-pituitary-adrenal (HPA) axis during viral infection. *Viral Immunol*. 2005;18:41–78.
52. Strain WD, Jankowski J, Davies A, et al. Development of an objective risk stratification tool to facilitate workplace assessments of healthcare workers when dealing with the COVID-19 pandemic. Available at: <https://www.bma.org.uk/media/2768/bma-covid-19-risk-assessment-tool-july2020.pdf>. Accessed 26th January 2021.
53. Struja T, Briner L, Meier A, et al. Diagnostic accuracy of basal cortisol level to predict adrenal insufficiency in cosyntropin testing: results from an observational cohort study with 804 Patients. *Endocr Pract*. 2017;23:949–961.

AU: Please do not delete query boxes or remove line numbers; ensure you address each query in the query box. You may modify text within selected text or outside the selected text (as appropriate) without deleting the query.

54. Suurmond R, van Rhee H, Hak T. Introduction, comparison and validation of Meta-Essentials: a free and simple tool for meta-analysis. *Res Synth Methods*. 2017;8:537–553.
55. Sytsma TT, Greenlund LK, Greenlund LS. Joint corticosteroid injection associated with increased influenza risk. *Mayo Clin Proc Innov Qual Outcomes*. 2018;2:194–198.
56. Tuncer S, Bariskaner H, Yosunkaya A, Reisli R. Systemic effects of epidural betamethasone injection. *Pain Clin*. 2004;16:311–315.
57. Varadé J, Magadán S, González-Fernández A. Human immunology and immunotherapy: main achievements and challenges. *Cell Mol Immunol*. 2021;18:805–828.
58. Versus Arthritis. The state of musculoskeletal health 2019. 2019. Available at: <https://www.versusarthritis.org/about-arthritis/data-and-statistics/state-of-musculoskeletal-health-2019/>. Accessed 20th September 2020.
59. Ward A, Watson J, Wood P, Dunne C, Kerr D. Glucocorticoid epidural for sciatica: metabolic and endocrine sequelae. *Rheumatology (Oxford)* 2002;41:68–71.
60. Weyland A, Meyer G, Weyland W, Ensink F, Haack, D. Adrenal suppression following epidural corticosteroid administration for discogenic pain: Influence of injection site. *Eur J Anaesthesiol*. 1992;9:136–137.
61. World Health Organization. COVID-19 Strategic preparedness and response plan. Available at: <https://www.who.int/publications/m/item/covid-19-strategic-preparedness-and-response-plan>. Accessed 20th January, 2021.

AU: Please do not delete query boxes or remove line numbers; ensure you address each query in the query box. You may modify text within selected text or outside the selected text (as appropriate) without deleting the query.

62. World Health Organization. Influenza (seasonal) factsheet. Available at:

[https://www.who.int/news-room/fact-sheets/detail/influenza-\(seasonal\)](https://www.who.int/news-room/fact-sheets/detail/influenza-(seasonal)). Accessed 5th

February 2021.

63. World Health Organization. Musculoskeletal factsheet. Available at:

<https://www.who.int/news-room/fact-sheets/detail/musculoskeletal-conditions>. Accessed

19th September 2021.

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Legends

Fig. 1 PRISMA flowchart showing the studies that were included in our review.

Fig. 2 Forest plot shows morning 7-day serum cortisol (nmol/l) for the included studies or subgroups and for the pooled estimate. The very small study by Dubois et al. [13] ($n = 2$) was omitted owing to the effect of its very wide CI (-1204.50nmol/l to 1425.63 nmol/l) on the scale of the graph, but its data are included in the displayed pooled estimate.

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